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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/267,963	03/12/99	MIYAZONO	K	LUD-5539.1-C

024972
FULBRIGHT & JAWORSKI, LLP
666 FIFTH AVE
NEW YORK NY 10103-3198

HM22/0815

EXAMINER	
ROMEO, D	
ART UNIT	**PAPER NUMBER**
1647	9

DATE MAILED: 08/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/267,963	Miyazano et al.
Examiner	**Group Art Unit**
David S. Romeo	1647

☒ Responsive to communication(s) filed on *1 Jun 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *14-20 and 28* is/are pending in the application.

Of the above, claim(s) *17 and 19* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *14-16, 18, 20, and 28* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *14-20 and 28* are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

2. The amendment filed 06/01/00 (Paper No. 7) has been entered. Claims 14-20, 28 are pending.

3. Applicant's election of group III, claims 14-20, 28 to the extent they read on methods which inhibit Smad1 or Smad5 phosphorylation, in Paper No. 7 is acknowledged. Applicant's election of an antibody which binds TGF-β as the species in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 17, 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

5. Claims 14-16, 18, 20, 28 are being examined to the extent they read upon the elected invention and/or species.

6. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). When a nonprovisional application (other than a CPA) is entitled under 35 U.S.C. 120 to an earlier U.S. effective filing date, a statement such as "This is a division (continuation, continuation-in-part) of Application No. ---, filed ---" should appear as the first sentence of the description, except in the case of design applications where it should appear as set forth in MPEP § 1504.20. Status of nonprovisional parent applications (whether it is patented or abandoned) should also be included. If a parent application has become a patent, the expression, "Patent No. _ _ " should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

8. The request for a corrected filing receipt filed 07/15/99 is acknowledged. It is unclear if the instant application is C-I-P of both earlier filed applications, or if it is only a C-I-P of one or the other. Appropriate clarification is requested.

9. The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. The specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Sequences are disclosed in Figures 1, 2, 3 without the appropriate sequence identifier, i.e. SEQ ID NO:. Applicant may bring the application into compliance by amending either the Figures or the "Brief Description of the Drawings" to recite the appropriate sequence identifier. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented

sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing."

Correction is required.

10. Figure 3 is presented on separate panels. 37 C.F.R. § 1.84 (u) (1) states that partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. View numbers must be preceded by the abbreviation "FIG." Thus, the separate panels should be renumbered FIG. 3A, FIG. 3B, etc. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (u) (1), the Brief Description of the Drawings and the rest of the specification must be amended accordingly.

11. The computer readable form of the sequence listing has been entered after correction of minor errors in the CRF by the Scientific and Technical Information Center staff. The Current Application Data section was edited with the actual current number.

12. With respect to the application of prior art, only the 09039177 application to which priority is claimed under 35 USC 120 describes the invention now claimed in the manner required

by 35 USC 112, first paragraph. The claims are not accorded benefit of any of the earlier filing dates.

Claim Rejections - 35 USC § 112

13. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite because it is unclear what binding is inhibited. It is suggested that the claim recite "binding of TGF-β to Alk1".

Claim 20 is indefinite over the recitation of "TGF receptor" because it is unclear which receptor is intended. The metes and bounds of the claim(s) are not clearly set forth. It is suggested that the claim recite "TGF-β receptor".

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 14-16, 18, 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi (u9)[1]. Takahashi teaches a method comprising contacting a human umbilical vein endothelial cell (HUVEC) with anti-transforming growth factor-β 1 neutralizing antibody. An HUVEC expresses a gene expression of which is activated by phosphorylated Smad1 or phosphorylated Smad5. An HUVEC presents Alk1 on its surfaces. An anti-transforming growth factor-β1 neutralizing antibody would interfere with TGF-β-mediated phosphorylation of Smad1 and inhibit the binding of TGF-β to Alk1. Anti-transforming growth factor-β 1 neutralizing antibody would inhibit the TGF-β-induced binding of Samd1 or Smad5 to Alk1 and would inhibit the TGF-β-induced interaction of Smad1 or Smad5 with a type II, TGF-β receptor.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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[1]References cited by the examiner are in an alphanumeric format, such as "a1", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

17. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hopkins (v9) in view of Kokame (w9). Hopkins teaches the platelet release reaction is an integral part of thrombosis. Platelet lysates induced PAI-1 mRNA. Hopkins teaches a method of identifying a gene whose activation is effected by TGF-β comprising contacting a first sample of cells with platelet lysates and measuring the increase in PAI-1 protein and comparing this level of PAI-1 protein with the level of PAI-1 protein produced by a second sample of cells contacted with platelet lysates and neutralizing antibodies to TGF-β. See Abstract. Hopkins does not teach a method a method of identifying a gene whose activation is effected by TGF-β comprising contacting a first sample of cells with platelet lysates in the presence of neutralizing antibodies to TGF-β, removing transcripts of said cells, and comparing said transcripts with transcripts from a second sample of cells contacted with platelet lysates in the absence of neutralizing antibodies to TGF-β. Kokame teaches that an elevated level of homocysteine is associated with arteriosclerosis and thrombosis. Kokame uses differential display to study the mechanisms by which homocysteine may promote vascular diseases. See abstract. The differential display technique involves comparing transcripts from a first sample of cells in the absence of a stimulus with transcripts from a second sample of cells in the presence of the stimulus, wherein any difference there between are transcripts whose activation is effected by the stimulus. See page 29660. It is apparent from Kokame that HUVECs are a model to be used for in vitro studies of vascular disease. Studies of novel gene transcripts are required to reveal the underlying mechanisms of

homocysteine-induced vascular injury (page 29665, column 1, full paragraph 1). Kokame does not teach a method of identifying a gene whose activation is effected by TGF-β comprising contacting a first sample of cells with platelet lysates in the presence of neutralizing antibodies to TGF-β, removing transcripts of said cells, and comparing said transcripts with transcripts from a second sample of cells contacted with platelet lysates in the absence of neutralizing antibodies to TGF-β. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to contact a first sample of cells with platelet lysates and measure the increase in PAI-1 protein and comparing this level of PAI-1 protein with the level of PAI-1 protein produced by a second sample of cells contacted with platelet lysates and neutralizing antibodies to TGF-β, as taught by Hopkins, and to modify that teaching by contacting a first sample of HUVECs with platelet lysates and removing transcripts from said first sample and comparing these transcripts with the transcripts a second sample of HUVECs contacted with platelet lysates and neutralizing antibodies to TGF-β, using the differential display technique, as taught by Kokame, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to study the role of TGF-β-induced novel gene transcripts underlying mechanisms of platelet-induced vascular injury or diseases such as thrombosis. HUVECs are cells which express and phosphorylate Smad1 or Smad5. A neutralizing antibody to TGF-β is an agent that inhibits phosphorylation of Smad1 or Smad5. Any differences in transcripts between the presence and absence of neutralizing antibodies to

TGF-β are transcripts of genes whose activation is effected by phosphorylation of Smad1 or Smad5. The invention is prima facie obvious over the prior art.

Conclusion

18. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Romeo
Primary Examiner
August 13, 2000